## ORIGINAL INVESTIGATION

# Comparison of heart failure risk and medical costs between patients with type 2 diabetes mellitus treated with dapagliflozin and dipeptidyl peptidase-4 inhibitors: a nationwide population-based cohort study

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## Abstract

**Background:** Dapagliflozin is one of the novel glucose-lowering agents, which has recently been reported to reduce the risk of hospitalization for heart failure (hHF). The present study aimed to compare the differences between the risk of hHF after using dapagliflozin and dipeptidyl peptidase-4 inhibitors (DPP-4i) as second-line drugs for the treatment of type 2 diabetes mellitus using the latest nationwide population data in Korea. Additionally, we aimed to examine the impact of clinical outcomes on direct medical costs in the two groups.

**Methods:** The present population-based, retrospective cohort study was conducted using the nationwide claims data between September 01, 2014 and June 30, 2018. New users of dapagliflozin and DPP-4i were identified from the database and the differences in patients' characteristics between the two groups were analyzed using propensity score-weighted analysis. Cox proportional hazards regression analysis was used to estimate the risk of hHF. A simple model was used for the estimation of direct medical costs for 3 years.

**Results:** In total, 23,147 patients in the dapagliflozin group and 237,187 patients in the DPP-4i group were selected for the analysis. The incidence rates of hHF were 3.86 and 6.79 per 1000 person-years in the dapagliflozin and DPP-4i groups, respectively. In the entire study population, the hazard ratio for hHF in the dapagliflozin group compared to the DPP-4i group was 0.58 (95% confidence interval 0.46–0.74), with 0.55 (95% confidence interval 0.41–0.74) among patients with underlying cardiovascular disease and 0.66 (95% confidence interval 0.46–0.95) among patients without underlying cardiovascular disease. The direct medical costs were $57,787 lower in the dapagliflozin group than in the DPP-4i group for 3 years.

**Conclusions:** This study showed that dapagliflozin lowers the risk for hHF and subsequently reduces direct medical costs compared to DPP-4i. The protective effect against hHF was more evident among patients with underlying cardiovascular disease.

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## Background

Type 2 diabetes mellitus (T2DM), a classic metabolic disorder, is consistently on the rise globally and is highly prevalent in Korea, with a prevalence of 14.4% among adults aged $\geq 30$ years and 29.8% among adults aged $\geq 65$ years as of 2016 [1]. Diabetes mellitus (DM) is known to exacerbate the clinical state of patients with heart failure (HF) and is associated with all-cause and cardiovascular mortality [2]. Further, HF with reduced ejection fraction (HFrEF) is used as an independent predictor of the treatment outcomes in T2DM [3, 4]. The percentage of patients with HF among the T2DM participants recruited in recent clinical trials ranged from 10 to 28% [5–12]. T2DM is known as an independent risk factor for HF incidence [13], and the incidence of HF was 2.5 times higher in the T2DM group than the non-T2DM group in a retrospective cohort study that followed-up with the patients for 72 months [14]. Therefore, HF management in patients with T2DM is a clinically important issue.

In general, current guidelines for T2DM treatment recommend metformin as the first-line therapy, and if appropriate blood glucose regulation is not achieved with monotherapy, a combination therapy with additional drugs is recommended [15–17]. Recently updated guidelines recommend sodium glucose co-transporter 2 inhibitors (SGLT-2i) or glucagon-like peptide 1 (GLP-1) receptor agonist treatment as first-line in patients with established cardiovascular disease (CVD) and newly diagnosed T2DM [18]. In Korea, more than 70% of the patients with DM were prescribed combination therapy consisting of more than two drugs in 2016, among which, 56% of the combinations involved metformin and dipeptidyl peptidase-4 inhibitors (DPP-4i) [1]. This suggests that DPP-4i is the second most common drug used after metformin. On the other hand, the use of SGLT-2i, a recently introduced DM medication beginning with dapagliflozin, is consistently on the rise since their inclusion in the health insurance coverage in Korea. Though only 3% of the patients prescribed two-drug therapy were prescribed with metformin and SGLT-2i in 2016 [1], the use of SGLT-2i, owing to the drug's cost, in the following 3 years increased fourfold than that in 2016 [19].

However, a controversy regarding the potential association between DPP-4i, which is the most widely used drug as a second-line therapy, and HF exists. While alogliptin, vildagliptin, sitagliptin, and linagliptin were not found to significantly increase the risk for HF [6–9], saxagliptin has been reported to significantly increase the risk of HF [5]. On the contrary, SGLT-2i, another second-line drug for DM, has been reported to lower the risk of HF [10–12]. In addition to randomized controlled trials, several studies using real-world evidence in actual clinical environments have reported such trends [20–26].

The risk of HF among patients with DM is an important determining factor for choosing drugs in clinical practice. Reduced HF risk, as a clinical outcome of drug therapy, is associated not only with improved quality of life but also with lower medical costs. As the soaring medical cost is affecting governments' and hospitals' decision-making process, cost must be taken into consideration while making choices in a clinical setting. Both clinical and economic outcomes have become an important factor for choosing medications for the highly prevalent DM in today's aging society.

Economical evaluation of DPP-4i and SGLT-2i, including dapagliflozin, as a second-line therapy for DM in the UK and US has shown that SGLT-2i is cost-effective and reduces the medical costs [27–29]. However, the results of pharmaco-economical evaluations vary according to the health insurance or healthcare service systems across countries, so it is difficult to directly cite the results reported in other countries. Therefore, country-specific assessment of the economic outcomes of the new class of DM drug, dapagliflozin, is necessary.

Consequently, the present study aimed to compare the differences in the risk of hospitalization due to HF between the dapagliflozin group, which is the first in a new class of SGLT-2i licensed in Korea, and the DPP-4i group, which are the most widely used second-line drugs for T2DM, using the latest real-world nationwide population data in Korea. Additionally, we aimed to examine the impact of clinical outcomes on medical costs in the two groups from an economic perspective.

## Methods

### Data source

A population-based cohort study was conducted using the claims data between September 01, 2014 and June 30, 2018. The data were retrieved from the Health Insurance Review & Assessment services, a government-affiliated agency, which reviews and assesses healthcare costs and service quality, as well as operates healthcare information system to support research [30]. This database contains longitudinal claims information including medical diagnoses, procedures, hospitalizations, physician visits,

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and prescription records of approximately 50 million Koreans. The diagnoses were coded according to the International Classification of Diseases, Tenth Revision (ICD-10).

Patients were not directly involved in the research, and only the secondary electronic database was used for the analysis. Informed consent was not required due to the retrospective nature of the study and the database maintained the anonymity of sampled individuals. This study was approved by the Cha University Institutional Review Board (Protocol ID: 1044308-201812-HR-060-01).

## Study population
Patients were eligible for inclusion in the study if they met the following criteria: had a diagnosis of T2DM (ICD-10, E11) and were aged 18–75 years between September 01, 2015 and August 31, 2016, and had $\geq 1$ prescription of dapagliflozin or DPP-4i during the same period. The date of first prescription of dapagliflozin or DPP-4i was considered as the entry date in the study cohort. To include new users of dapagliflozin or DPP-4i, the patients who had been prescribed dapagliflozin or DPP-4i within 365 days prior to the cohort entry (baseline period) were excluded. Patients using other SGLT-2i and GLP-1 receptor agonists during the baseline period were also excluded. Patients with acute cardiovascular event (e.g., hospitalization with a diagnosis of HF, myocardial infarction, and ischemic stroke) within 8 weeks prior to the cohort entry were excluded. We also excluded all patients with a diagnosis of cancer, human immunodeficiency virus infection, or end stage renal disease at any time prior to the cohort entry, including those with entire period of follow-up after the cohort entry. Patients with a diagnosis of type 1 DM or gestational diabetes during the baseline period were also excluded.

## Comparison of clinical outcomes
The primary outcome was the first incidence of hospitalization for HF (hHF) (admission with ICD-10 code I50) after the index date. Each patient was followed-up from cohort entry until the first incidence of the following: hHF, treatment switch or discontinuation, i.e., a gap of > 30 days between prescription fill dates, death from any cause, or the end of the study duration (June 30, 2018).

The baseline characteristics, including sex and age, were assessed for patients in each group. To address comorbidities, patients with one of the following diagnoses within a year prior to the date of cohort entry were identified: microvascular complications of diabetes, including nephropathy, neuropathy, retinopathy; hypertension; dyslipidemia; chronic kidney disease; CVD, including myocardial infarction, other ischemic heart disease, ischemic stroke, hemorrhagic stroke,

peripheral artery occlusive disease, coronary revascularization procedures (coronary artery bypass graft, percutaneous coronary intervention), HF, and atrial fibrillation; hypoglycemia; asthma; chronic obstructive pulmonary disease; connective tissue disease; pancreatitis; osteoporosis; alcohol intake; smoking habit; and obesity. For concomitant medications, patients with one of the following drug prescriptions within 180 days prior to the date of cohort entry were identified: anti-hyperglycemic agents, including metformin, sulfonylurea, thiazolidinediones, alpha-glucosidase inhibitor, meglitinide, insulin; diuretics, including loop diuretics, thiazide, aldosterone antagonist, potassium sparing diuretics; anti-hypertensive agents, including calcium channel blocker, angiotensin converting enzyme inhibitor, angiotensin II receptor blocker, beta blocker, alpha blocker; digoxin; aspirin; P2Y12 inhibitor; warfarin; non-vitamin K antagonist oral anticoagulant; and lipid-lowering agents, including statin, fibrate, ezetimibe. Further, the following healthcare utilization data were identified as covariates: visit to cardiology within 30 days prior to the date of cohort entry; hospitalization within 30 days prior to the date of cohort entry; hospitalization within 30–365 days prior to the date of cohort entry; visit to the emergency department within 365 days prior to the date of cohort entry.

Standardized differences were used to examine the baseline differences between the dapagliflozin group and DPP-4i group [31]. The rate of hHF was computed for each group. The hazard ratios (HR) and 95% confidence interval (CI) for hHF in the dapagliflozin group and DPP-4i group were computed using the Cox proportional hazards model. The incidence of hHF in each group was shown using the Kaplan–Meier curve. The baseline differences between the two groups were adjusted using propensity scores. To count for the odds for dapagliflozin to be prescribed, propensity scores were computed using the information of all covariates evaluated as the baseline characteristics—age, sex, comorbidities, concomitant medications and healthcare utilization. Propensity score-weighted analysis was performed to create a pseudo-population with equal distribution of covariates between the DPP-4i group and dapagliflozin group; these pseudo-populations of the DPP-4i and dapagliflozin groups were compared to compute the risk of hHF in each group [32–34]. Subgroup analysis was performed to analyze the risk of an event according to cardiovascular comorbidity prior to the date of cohort entry. During the sensitivity analysis, we performed intention-to-treat analysis, which assumes that the drugs prescribed at the time of cohort entry were used throughout the follow-up period, to compute the risk of hHF.

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## Comparison of economic outcomes

To analyze direct medical costs that reflect clinical outcomes, we used a model that incorporated changes in the patients' health status over 3 years (Fig. 1). This model was simulated using annual medical cost corresponding to each health status and health status transition probability. We analyzed medical costs for 3 years by including 1000 participants for each cohort in the study.

In total, six health statuses were used in this model: hHF: first incidence of hHF; no hHF: no onset of hHF; DM with HF: survived from hHF and is continuing DM and HF treatment; HF death: death following hHF; DM without HF: survived without the onset of HF and is continuing DM treatment; and Other death: death without diagnosis of HF.

Health status transition probability was calculated using the HR obtained from clinical outcome analysis. The incidence rate of hHF for DPP-4i group was used to convert to 1-year probability, and that for the dapagliflozin group was calculated by multiplying HR to the incidence rate of the DPP-4i group. For estimating the probability of mortality based on the diagnosis of hHF, the mortality rate of DPP-4i group was calculated by following-up the participants from cohort entry to death or study termination (June 2018), and the HR for death for the dapagliflozin group was computed against the death rate of DPP-4i group using propensity score weighting.

Based on the follow-up of the entire study population from cohort entry until death or study termination (June 2018), the median per patient medical cost/month was identified. Medical costs were computed according to the occurrence of an event during follow-up and death/ survival. The annual medical cost of survivors continuing the treatment was calculated by multiplying the monthly treatment cost by 12, and that of dead patients was calculated by multiplying the monthly treatment cost by 6, under the assumption that they survived for 6 months in a year. Further, as we used insurance claims data for this analysis, we applied the non-coverage rate by disease to estimate patients' out-of-pocket costs. The non-coverage rate for patients with heart disease as of 2018 (6.3%) was applied for the hHF patients, and the non-coverage rate for the entire health insurance recipient population (16.6%) was applied for the non-hHF patients [35]. Cost is presented as US dollars, which was calculated on the basis of annual average currency exchange rate for 2018 (1165 KRW = 1\$).

The incidence of hHF among patients undergoing treatment was utilized for basic analysis, while the incidence of hHF and HR of intend-to-treat patients was used for the sensitivity analysis. Analyses were performed using the SAS 9.4 version (SAS Institute Inc, Cary, NC, USA), and survival curves were drawn using R software 3.1.2 version (R Foundation for Statistical Computing, Vienna, Austria).
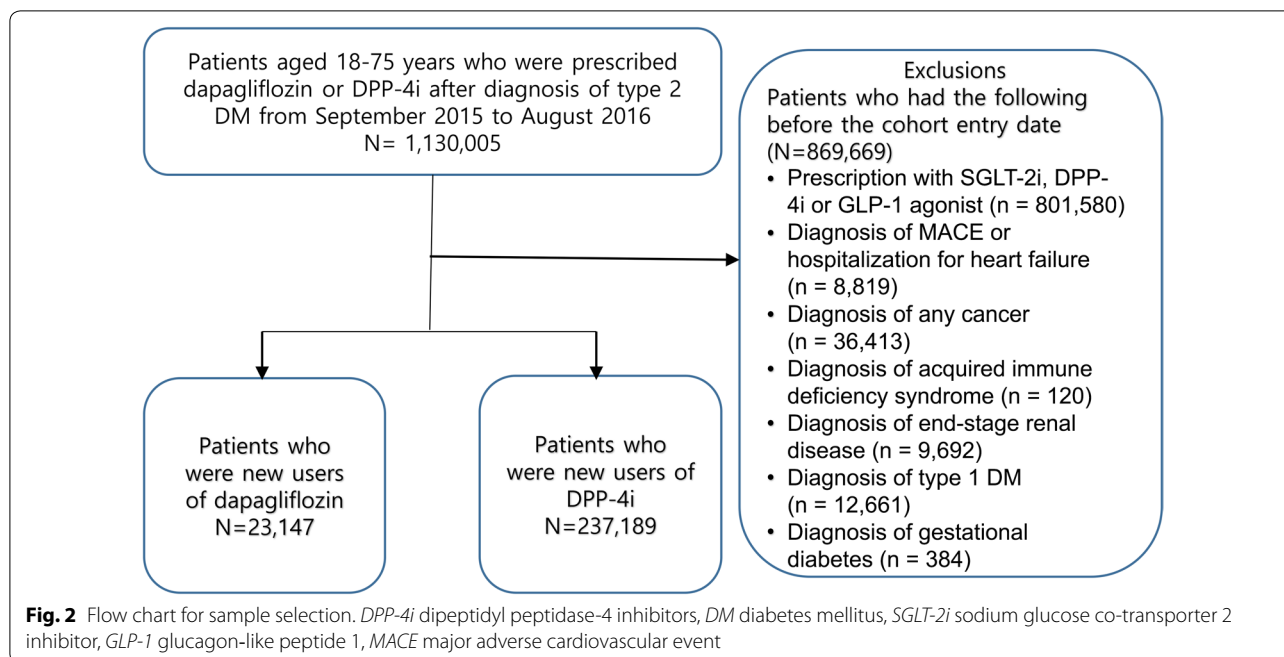
## Results

### Study population and patient characteristics

In total, 1,130,005 patients were prescribed DPP-4i or dapagliflozin after the diagnosis of T2DM during the recruitment period from September 2015 to August 2016. After excluding 869,669 patients per the exclusion criteria, 23,147 patients were new dapagliflozin users, and 237,187 patients were new DPP-4i users (Fig. 2).

Prior to the propensity score weighting, dapagliflozin group had younger participants and a lower percentage of men as compared to the DPP-4i group. The number of patients with a history of admission within 30 days prior to the index date was greater in the DPP-4i group, while the percentage of patients who recently visited a
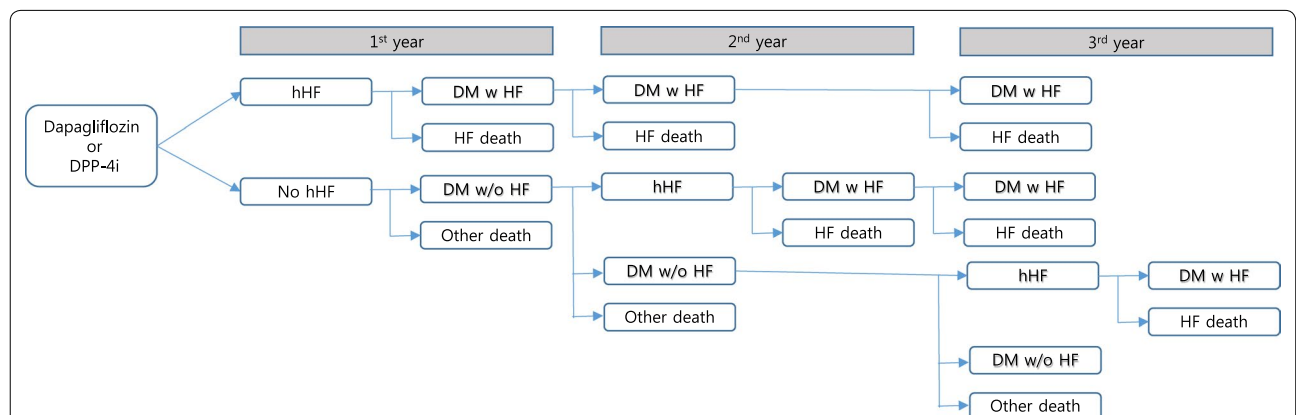


**Fig. 1** Schematic diagram of health status for cost analysis. *DPP-4i* dipeptidyl peptidase-4 inhibitors, *hHF* hospitalization for heart failure, *DM w HF* diabetes mellitus with heart failure, *DM w/o HF* diabetes mellitus without heart failure, *HF death* death after diagnosis of heart failure, *other death* death without diagnosis of heart failure

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**Fig. 2** Flow chart for sample selection. *DPP-4i* dipeptidyl peptidase-4 inhibitors, *DM* diabetes mellitus, *SGLT-2i* sodium glucose co-transporter 2 inhibitor, *GLP-1* glucagon-like peptide 1, *MACE* major adverse cardiovascular event

cardiologist was greater in the dapagliflozin group. Dyslipidemia was the only comorbidity that showed a significant difference at baseline between the two groups, with an SD of $\geq 10\%$, and the prevalence of dyslipidemia was higher in the dapagliflozin group than in the DPP-4i group. The percentage of patients using a statin was also higher in the dapagliflozin group as compared to the DPP-4i group. Though the number of patients taking anti-hyperglycemic medications was higher in the DPP-4i group, the number of patients using insulin was higher in the dapagliflozin group. However, all variables were well balanced between the two groups after propensity score weighting (Table 1).

**Comparison of clinical outcomes**
The total number of hHF events during an average follow-up period of 16.3 months (dapagliflozin 14.7 months, DPP-4i 16.5 months) was 4537; and the incidence rate in the dapagliflozin and DPP-4i groups was 3.86 and 6.79 per 1000 person-year, respectively. In the entire study population, the adjusted HR (aHR) for hHF in the dapagliflozin group as compared to the DPP-4i group was 0.58 (95% CI 0.46–0.74), and was 0.55 (95% CI 0.41–0.74) among patients with underlying CVD and 0.66 (95% CI 0.46–0.95) among patients without underlying CVD (Table 2 and Fig. 3). In the intend-to-treat analysis, the dapagliflozin group also had a significantly lower risk for hHF (aHR: 0.70, 95% CI 0.60–0.82) (Table 2) than the DPP-4i group.

**Comparison of economical outcomes**
The annual average treatment cost for patients who survived after hHF and continued treatment was $4964 per patient, which was approximately six times higher than that for patients without hHF. The annual medical cost for patients who died after hHF was $6718 per patient, which was approximately 2.3 times higher than that for patients who died without hHF (Table 3). Table 4 shows the parameters used in the cost analysis model that utilized HR for hHF and death probabilities according to hHF. Direct medical costs, calculated using the model for 1000 patients per drug group, were $2,542,221 for the dapagliflozin group and $2,600,008 for the DPP-4i group over 3 years, thereby indicating that the cost was $57,787 lower in the dapagliflozin group. The difference increased to $177,580 among patients with underlying CVD, which was approximately seven times higher than that among the patients without underlying CVD (Table 5). In the sensitivity analysis using the HR of intend-to-treat patients, the direct medical cost was $48,097 lower in the dapagliflozin group over 3 years, and the reduction of direct medical cost was approximately 5.7 times greater among patients with underlying CVD as compared to those without underlying CVD (Table 5).

**Discussion**
The present study showed that dapagliflozin lowered the risk for hHF and subsequently lowered direct medical costs as compared to DPP-4i in patients with T2DM.

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**Table 1 Baseline characteristics of the study population before and after propensity score weighting**

| | Entire population | | | Propensity score weighted population | | |
|---|---|---|---|---|---|---|
| | Dapagliflozin (N = 23,147) | DPP-4i (N = 237,189) | Standardized difference | Dapagliflozin (N = 23,147) | DPP-4i (N = 237,189) | Standardized difference |
| Age (years), mean (SD) | 52.6 (11.50) | 56.9 (10.88) | 0.38 | 52.6 (11.50) | 52.7 (3.59) | 0.00 |
| Men | 12,557 (0.54) | 141,542 (0.60) | 0.11 | 12,557 (0.54) | 12,584 (0.54) | 0.00 |
| Microvascular complication of diabetes | | | | | | |
| Nephropathy | 1951 (0.08) | 15,372 (0.06) | 0.07 | 1951 (0.08) | 1970 (0.09) | 0.00 |
| Neuropathy | 2836 (0.12) | 26,453 (0.11) | 0.03 | 2836 (0.12) | 2840 (0.12) | 0.00 |
| Retinopathy | 3641 (0.16) | 30,890 (0.13) | 0.08 | 3641 (0.16) | 3623 (0.16) | 0.00 |
| Cardiovascular disease | | | | | | |
| Hemorrhagic stroke | 86 (0.00) | 1495 (0.01) | 0.04 | 86 (0.00) | 85 (0.00) | 0.00 |
| Other ischemic heart disease | 3498 (0.15) | 28,245 (0.12) | 0.09 | 3498 (0.15) | 3521 (0.15) | 0.00 |
| Ischemic stroke | 752 (0.03) | 10,022 (0.04) | 0.05 | 752 (0.03) | 755 (0.03) | 0.00 |
| Myocardial infarction | 291 (0.01) | 2287 (0.01) | 0.03 | 291 (0.01) | 294 (0.01) | 0.00 |
| Heart failure | 817 (0.04) | 6895 (0.03) | 0.04 | 817 (0.04) | 833 (0.04) | 0.00 |
| Peripheral artery occlusive disease | 158 (0.01) | 1875 (0.01) | 0.01 | 158 (0.01) | 160 (0.01) | 0.00 |
| Coronary artery bypass graft | 6 (0.00) | 107 (0.00) | 0.01 | 6 (0.00) | 6 (0.00) | 0.00 |
| Percutaneous coronary intervention | 407 (0.02) | 3552 (0.01) | 0.02 | 407 (0.02) | 417 (0.02) | 0.00 |
| Comorbidities[a] | | | | | | |
| Obesity | 103 (0.00) | 447 (0.00) | 0.05 | 103 (0.00) | 100 (0.00) | 0.00 |
| Osteoporosis | 1602 (0.07) | 21,719 (0.09) | 0.08 | 1602 (0.07) | 1605 (0.07) | 0.00 |
| Atrial fibrillation | 370 (0.02) | 3829 (0.02) | 0.00 | 370 (0.02) | 376 (0.02) | 0.00 |
| Hypertension | 13,992 (0.60) | 135,909 (0.57) | 0.06 | 13,992 (0.60) | 14,001 (0.61) | 0.00 |
| Alcohol intake | 1014 (0.04) | 13,260 (0.06) | 0.06 | 1014 (0.04) | 1016 (0.04) | 0.00 |
| Smoking habit | 38 (0.00) | 223 (0.00) | 0.02 | 38 (0.00) | 38 (0.00) | 0.00 |
| Asthma | 2914 (0.13) | 28,920 (0.12) | 0.01 | 2914 (0.13) | 2911 (0.13) | 0.00 |
| Chronic kidney disease | 167 (0.01) | 3583 (0.02) | 0.08 | 167 (0.01) | 171 (0.01) | 0.00 |
| COPD | 1092 (0.05) | 12,879 (0.05) | 0.03 | 1092 (0.05) | 1096 (0.05) | 0.00 |
| Connective tissue disease | 841 (0.04) | 9117 (0.04) | 0.01 | 841 (0.04) | 844 (0.04) | 0.00 |
| Pancreatitis | 374 (0.02) | 3999 (0.02) | 0.01 | 374 (0.02) | 367 (0.02) | 0.00 |
| Hypoglycemia | 535 (0.02) | 5450 (0.02) | 0.00 | 535 (0.02) | 534 (0.02) | 0.00 |
| Dyslipidemia | 19,361 (0.84) | 183,745 (0.77) | 0.16 | 19,361 (0.84) | 19,342 (0.84) | 0.00 |
| Medication use | | | | | | |
| Anti-diabetic agent | | | | | | |
| Number of drugs | 2.0 (0.64) | 2.1 (0.64) | 0.24 | 2.0 (0.64) | 2.0 (0.20) | 0.00 |
| Metformin | 19,334 (0.84) | 211,407 (0.89) | 0.16 | 19,334 (0.84) | 19,313 (0.83) | 0.00 |
| Sulfonylurea | 8859 (0.38) | 102,332 (0.43) | 0.10 | 8859 (0.38) | 8907 (0.39) | 0.00 |
| Thiazolidinediones | 2508 (0.11) | 21,575 (0.09) | 0.06 | 2508 (0.11) | 2512 (0.11) | 0.00 |
| Meglitinide | 198 (0.01) | 1724 (0.01) | 0.01 | 198 (0.01) | 202 (0.01) | 0.00 |
| α-glucosidase inhibitor | 967 (0.04) | 10,930 (0.05) | 0.02 | 967 (0.04) | 984 (0.04) | 0.00 |
| Insulin | 4456 (0.19) | 32,334 (0.14) | 0.15 | 4456 (0.19) | 4438 (0.19) | 0.00 |
| Anti-hypertensive drugs | | | | | | |
| Calcium channel blocker | 6356 (0.27) | 64,718 (0.27) | 0.00 | 6356 (0.27) | 6337 (0.27) | 0.00 |
| ACEI | 578 (0.02) | 4238 (0.02) | 0.05 | 578 (0.02) | 590 (0.03) | 0.00 |
| β-blocker | 2101 (0.09) | 18,425 (0.08) | 0.05 | 2101 (0.09) | 2111 (0.09) | 0.00 |
| ARB | 10,482 (0.45) | 100,108 (0.42) | 0.06 | 10,482 (0.45) | 10,466 (0.45) | 0.00 |
| α-blocker | 154 (0.01) | 1546 (0.01) | 0.00 | 154 (0.01) | 153 (0.01) | 0.00 |
| Diuretics | | | | | | |
| Thiazide | 3178 (0.14) | 31,487 (0.13) | 0.01 | 3178 (0.14) | 3166 (0.14) | 0.00 |
| Aldosterone antagonist | 445 (0.02) | 4181 (0.02) | 0.01 | 445 (0.02) | 452 (0.02) | 0.00 |

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**Table 1  (continued)**

| | Entire population | | | Propensity score weighted population | | |
|---|---|---|---|---|---|---|
| | Dapagliflozin (N = 23,147) | DPP-4i (N = 237,189) | Standardized difference | Dapagliflozin (N = 23,147) | DPP-4i (N = 237,189) | Standardized difference |
| Loop diuretics | 765 (0.03) | 9539 (0.04) | 0.04 | 765 (0.03) | 777 (0.03) | 0.00 |
| Potassium sparing diuretics | 13 (0.00) | 155 (0.00) | 0.00 | 13 (0.00) | 13 (0.00) | 0.00 |
| Warfarin | 128 (0.01) | 1461 (0.01) | 0.01 | 128 (0.01) | 133 (0.01) | 0.00 |
| NOAC | 98 (0.00) | 1384 (0.01) | 0.02 | 98 (0.00) | 101 (0.00) | 0.00 |
| Aspirin | 4872 (0.21) | 51,286 (0.22) | 0.01 | 4872 (0.21) | 4909 (0.21) | 0.00 |
| P2Y12 inhibitor | 2643 (0.11) | 23,930 (0.10) | 0.04 | 2643 (0.11) | 2667 (0.12) | 0.00 |
| Digoxin | 145 (0.01) | 1845 (0.01) | 0.02 | 145 (0.01) | 147 (0.01) | 0.00 |
| Lipid-lowering agents | | | | | | |
| Statin | 12,354 (0.53) | 113,483 (0.48) | 0.11 | 12,354 (0.53) | 12,358 (0.53) | 0.00 |
| Ezetimibe | 1556 (0.07) | 11,881 (0.05) | 0.07 | 1556 (0.07) | 1559 (0.07) | 0.00 |
| Fibrate | 1447 (0.06) | 11,964 (0.05) | 0.05 | 1447 (0.06) | 1454 (0.06) | 0.00 |
| Healthcare utilization | | | | | | |
| Cardiologist visit | 2116 (0.09) | 13,155 (0.06) | 0.14 | 2116 (0.09) | 2172 (0.09) | 0.01 |
| Emergency department visit | 1758 (0.08) | 18,209 (0.08) | 0.00 | 1758 (0.08) | 1761 (0.08) | 0.00 |
| Hospitalization (within 30 days)[b] | 1506 (0.07) | 29,675 (0.13) | 0.21 | 1506 (0.07) | 1509 (0.07) | 0.00 |
| Hospitalization (during 30–365 days)[c] | 3524 (0.15) | 37,400 (0.16) | 0.02 | 3524 (0.15) | 3548 (0.15) | 0.00 |

Data are presented as frequency (percentage), or mean (standard deviation)

*DPP-4i* Dipeptidyl-peptidase 4 inhibitor, *SD* standard deviation, *COPD* chronic obstructive pulmonary disease, *ACEI* angiotensin-converting-enzyme inhibitor, *ARB* angiotensin-2 receptor antagonist, *NOAC* Novel oral anticoagulant

[a] Confirmed by diagnosis code (International Classification of Diseases, 10th revision)

[b] Hospitalization within 30 days prior to index date

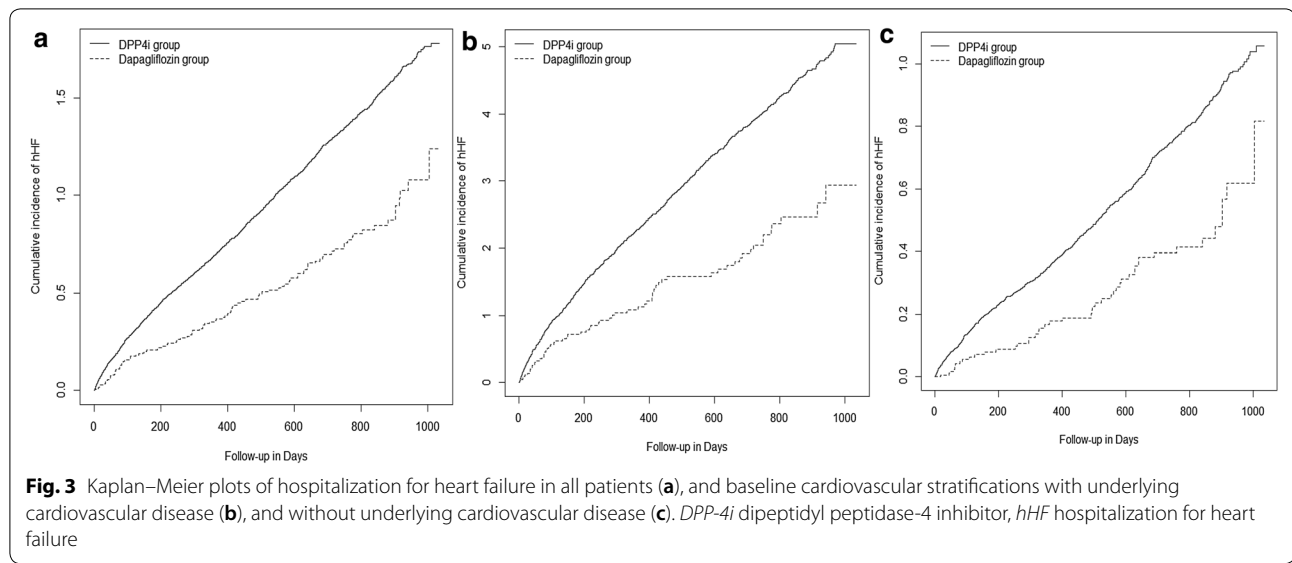[c] Hospitalization during 30–365 days prior to index date

**Table 2  The risk of hospitalization for heart failure of dapagliflozin group compared with DPP-4i group**

| | Dapagliflozin group | | | DPP-4i group | | | cHR | 95% CI | aHR | 95% CI |
|---|---|---|---|---|---|---|---|---|---|---|
| | No. of events | Person-year (PY) | Incidence (/1000PY) | No. of events | Person-year (PY) | Incidence (/1000PY) | | | | |
| On treatment analysis | | | | | | | | | | |
| Total | 110 | 28,478 | 3.86 | 2210 | 325,344 | 6.79 | 0.56 | 0.46–0.68 | 0.58 | 0.46–0.74 |
| CVD | 64 | 5605 | 11.42 | 1196 | 57,819 | 20.69 | 0.54 | 0.42–0.69 | 0.55 | 0.41–0.74 |
| Non-CVD | 46 | 22,873 | 2.01 | 1014 | 267,525 | 3.79 | 0.53 | 0.39-071 | 0.66 | 0.46–0.95 |
| Intention-to-treat analysis | | | | | | | | | | |
| Total | 267 | 54,145 | 4.93 | 4270 | 546,982 | 7.81 | 0.63 | 0.56–0.71 | 0.70 | 0.60–0.82 |
| CVD | 148 | 10,657 | 13.89 | 2084 | 93,600 | 22.26 | 0.62 | 0.53–0.74 | 0.66 | 0.53–0.81 |
| Non-CVD | 119 | 43,488 | 2.74 | 2186 | 453,382 | 4.82 | 0.57 | 0.47–0.68 | 0.74 | 0.58–0.94 |

*DPP-4i* Dipeptidyl-peptidase 4 inhibitor, *PY* person-year, *cHR* crude hazard ratio, *aHR* adjusted hazard ratio, *CI* confidence interval, *CVD* Patients with underlying cardiovascular disease, *Non-CVD* patients without underlying cardiovascular disease

Two large cardiovascular outcomes trials (CVOTs) of SGLT-2i—Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) and Canagliflozin Cardiovascular Assessment Study (CANVAS)—demonstrated consistent reduction in the incidence of hHF among patients with T2DM, although hHF was not a primary endpoint in these trials [10, 11]. In the Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58) study, treatment with dapagliflozin resulted in a lower rate of cardiovascular death or hHF (one of the primary outcomes) in patients with T2DM [12]. Moreover, a recent meta-analysis of these 3 CVOTs showed that SGLT-2i reduced the risk of hHF in patients

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**Fig. 3** Kaplan–Meier plots of hospitalization for heart failure in all patients (**a**), and baseline cardiovascular stratifications with underlying cardiovascular disease (**b**), and without underlying cardiovascular disease (**c**). *DPP-4i* dipeptidyl peptidase-4 inhibitor, *hHF* hospitalization for heart failure

**Table 3 Medical cost according to health status (USD/year/person)**

| Patient groups | Health status | Annual direct medical cost (USD) |
|---|---|---|
| All patients | DM with HF | 4964.0 |
| | HF death | 6718.1 |
| | DM without HF | 813.6 |
| | Other death[a] | 2919.5 |
| Patients with underlying CVD | DM with HF | 5321.5 |
| | HF death | 6615.5 |
| | DM without HF | 1286.5 |
| | Other death[a] | 2783.9 |
| Patients without underlying CVD | DM with HF | 4701.1 |
| | HF death | 6864.5 |
| | DM without HF | 743.2 |
| | Other death[a] | 2964.6 |

Data source: Claim data of the Health Insurance Review & Assessment services

*DM* Diabetes mellitus, *HF* heart failure, *CVD* cardiovascular disease

[a] Death without diagnosis of heart failure

**Table 4 Model inputs: probabilities of hospitalization for heart failure and death for dapagliflozin/DPP-4i treated patients**

| Patient groups | Base analysis | | Sensitivity analysis | |
|---|---|---|---|---|
| | Dapagliflozin | DPP-4i | Dapagliflozin | DPP-4i |
| All patients | | | | |
| hHF incidence | 0.0054 | 0.0078 | 0.0040 | 0.0068 |
| HF death | 0.0198 | 0.0253 | 0.0198 | 0.0253 |
| Other death | 0.0010 | 0.0013 | 0.0010 | 0.0013 |
| Patients with underlying CVD | | | | |
| hHF incidence | 0.0145 | 0.0220 | 0.0113 | 0.0205 |
| HF death | 0.0105 | 0.0243 | 0.0105 | 0.0243 |
| Other death | 0.0016 | 0.0024 | 0.0016 | 0.0024 |
| Patients without underlying CVD | | | | |
| hHF incidence | 0.0036 | 0.0048 | 0.0025 | 0.0038 |
| HF death | 0.0355 | 0.0264 | 0.0355 | 0.0264 |
| Other death | 0.0009 | 0.0010 | 0.0009 | 0.0010 |

Data source: Claim data of the Health Insurance Review & Assessment services

*DPP-4i* Dipeptidyl-peptidase 4 inhibitor, *hHF* hospitalization for heart failure, *HF* heart failure, *CVD* cardiovascular disease

with T2DM regardless of the presence of CVD or history of HF [36]. Previous CVOTs of SGLT-2i included T2DM patients with established CVD or at the high risk for CVD. However, the present study covered a wider range of nationwide population cohort including patients with and without CVD. Our results showed that dapagliflozin reduced the risk for hHF in patients with and without CVD, and the HF protective effect of dapagliflozin was more evident among patients with underlying CVD.

In the present study, we compared dapagliflozin, a first-in-class SGLT-2i, with DPP-4i, one of the most

widely used second-line oral anti-hyperglycemic agents in a real-world observational cohort. The findings of our study showed that the use of dapagliflozin reduced hHF as compared to DPP-4i. Our results are consistent with the results of previous observational studies, wherein, SGLT-2i was compared with other non-SGLT-2i oral anti-hyperglycemic agents [20–23], sulfonylureas and DPP-4i [24], or DPP-4i in a similar cohort [25]. A large Scandinavian cohort study also reported that SGLT-2i use compared with DPP-4i use was associated with a

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**Table 5  Direct medical costs (USD) for 3 years among dapagliflozin treated patients and DPP-4i treated patients**

| Patient groups | Treatment | Treatment year | | | Total |
|---|---|---|---|---|---|
| | | 1st year | 2nd year | 3rd year | |
| Base analysis | | | | | |
| All patients | Dapagliflozin | 832,312 | 847,560 | 862,349 | 2,542,221 |
| | DPP-4i | 844,608 | 870,883 | 884,517 | 2,600,008 |
| | Difference | 12,296 | 23,323 | 22,169 | 57,787 |
| Patients with underlying CVD | Dapagliflozin | 1,334,443 | 1,376,727 | 1,417,845 | 4,129,014 |
| | DPP-4i | 1,373,319 | 1,448,896 | 1,484,380 | 4,306,594 |
| | Difference | 38,876 | 72,169 | 66,535 | 177,580 |
| Patients without underlying CVD | Dapagliflozin | 755,451 | 764,393 | 772,895 | 2,292,739 |
| | DPP-4i | 760,709 | 774,577 | 782,840 | 2,318,126 |
| | Difference | 5258 | 10,184 | 9945 | 25,387 |
| Sensitivity analysis | | | | | |
| All patients | Dapagliflozin | 838,482 | 859,691 | 880,237 | 2,578,409 |
| | DPP-4i | 848,827 | 879,127 | 898,553 | 2,626,506 |
| | Difference | 10,345 | 19,436 | 18,317 | 48,097 |
| Patients with underlying CVD | Dapagliflozin | 1,347,676 | 1,402,655 | 1,455,945 | 4,206,275 |
| | DPP-4i | 1,379,600 | 1,460,981 | 1,508,597 | 4,349,179 |
| | Difference | 31,925 | 58,327 | 52,653 | 142,904 |
| Patients without underlying CVD | Dapagliflozin | 759,669 | 772,623 | 784,938 | 2,317,229 |
| | DPP-4i | 764,829 | 782,650 | 794,789 | 2,342,268 |
| | Difference | 5160 | 10,027 | 9851 | 25,039 |

*DPP-4i* Dipeptidyl-peptidase 4 inhibitor, *CVD* cardiovascular disease

reduced risk of HF, with similar HR to that in our study both in on-treatment analysis and intention-to-treat analysis. Moreover, the magnitude of the protective association between SGLT-2i and HF was larger in on-treatment analysis, suggesting that the HF protective effect of SGLT-2i could be stronger during the time that patients stay on the drug [26]. A network meta-analysis to compare the effect on CV outcomes among SGLT-2i, GLP-1 receptor agonist, and DPP-4i also reported that SGLT-2i show clear superiority in reducing hHF among the three new drug classes [37].

Our data provide information on the risk of hHF of dapagliflozin, not of all SGLT2i. The effects on hHF may differ between individual SGLT-2i, because not all SGLT-2i share the same pharmacokinetic properties [38]. A retrospective cohort study reported that dapagliflozin users had a significantly lower risk of HF as compared to empagliflozin users, and further studies are required to confirm the findings [39].

A recent placebo-controlled trial (DAPA-HF trial) showed that the risk of worsening HF or death from cardiovascular causes was lower among the HF patients with reduced ejection fraction who received dapagliflozin than those who received placebo, regardless of the presence or absence of diabetes [40]. Moreover, dapagliflozin reduced hHF both in patients with and without HFrEF

in the stratified analysis by baseline ejection fraction of DECLARE-TIMI 58 patients. [41]. Thus, the growing evidence is suggestive of HF protective effects of SGLT-2i. Several underlying mechanisms have been proposed to explain the HF protective effect of SGLT-2i, such as improvement in ventricular loading conditions through a reduction in preload and afterload, improvement in cardiac metabolism and bioenergetics, myocardial $Na^+/H^+$ exchange inhibition, reduction of necrosis and cardiac fibrosis and an alteration in adipokine production [42].

The recent consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) addresses the approaches to management of glycemia in patients with T2DM, with the goal of reducing complications and maintaining quality of life in the context of comprehensive cardiovascular risk management changed from the prior consensus statements, wherein, efficacy in reducing hyperglycemia, along with tolerability and safety were primary factors in glucose-lowering medication selection [16]. The recently updated consensus report by the ADA and the EASD suggested that SGLT-2i are recommended in patients with T2DM and HF, particularly those with HF with HFrEF, to reduce hHF, major adverse cardiovascular event, and CVD death [43]. Our study showed the superiority of dapagliflozin to DPP-4i, one of the most widely

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used oral hypoglycemic agents, in terms of HF protection in a real-world clinical setting and broad T2DM population, and in accordance with the current guideline, prior CVOTs, meta-analyses, and observation studies.

Our economical evaluation, based on a simulation on 1000 patients for each group, showed that the dapagliflozin group saved about $12,000 of medical costs in the first year, with a two-fold greater cost reduction in the second year as compared to the DPP-4i group. With the use of dapagliflozin, approximately $58,000 of medical cost was saved over 3 years, with a threefold greater cost reduction among patients with underlying CVD. Similar results were found in the sensitivity analysis on intend-to-treat patients, thereby confirming that dapagliflozin is highly effective in lowering hHF risk and cutting medical costs in patients with underlying CVD.

An analysis for cost-effectiveness of dapagliflozin, conducted in the UK, showed that dapagliflozin had an incremental cost-effectiveness ratio (ICER) of £6761 per quality adjusted life years (QALY) gained as compared to DPP-4i; based on which, dapagliflozin was found to be a cost-effective agent as an addition to the regimen for patients with DM whose blood glucose was not appropriately controlled with only metformin as compared to DPP-4i, which was the most widely used agent for the purpose [27]. The changes in HbA1c level and body weight for 1 year were used as the parameters for comparing clinical outcomes between the dapagliflozin and DPP-4i groups, and the authors claimed that the superior weight-loss effects of dapagliflozin were the underlying reasons for increased QALY. In a simulation of 30,000 patients for 40 years using a model, including the probability of DM complications in relation to weight loss and related QALY and cost, dapagliflozin was associated with £216 more cost and 0.032 increase of QALYs compared to DPP-4i. These findings were obtained on the basis of long-term simulation with weight loss as the major outcome amid a lack of long-term clinical outcome data and data on major DM complications associated with dapagliflozin and DPP-4i, which may lead to a difference from the results that reflect the real-world reports of CVD and renal complications. In contrast, we analyzed a simplified model for a relatively short time period (3 years), reflecting the clinical outcomes and cost values measured through real-world data analysis to minimize the influence of the limitations of economic analysis, such as excessive extrapolation and assumption.

In another economic evaluation conducted in Australia, decision analysis was applied to assess the cost-effectiveness of first-line combination dapagliflozin and metformin (first-line use) versus first-line metformin monotherapy followed by gradual addition of dapagliflozin over time (delayed use) [28]. Clinical outcomes were derived from a published observational study, CVD-REAL Nordic, and a Markov model was used to simulate the progress for 20 years. The Australia study showed that first-line use had an ICER of AUD $12,477 per QALY gained as compared to delayed use, even though first-line use of the combination is not recommended in the current guidelines [28]. Both UK and Australian studies have shown that dapagliflozin is not only effective compared to DPP-4i or delayed use, but also increases costs. This study did not analyze the ratio of the cost to the effectiveness, but showed the reduced the medical cost due to the improved clinical outcomes. Therefore, care should be taken to quantitatively compare and interpret the results of this study with other CE analysis.

Further, Garry et al. analyzed the medical costs between patients who used SGLT-2i and patients who used DPP-4i as second-line therapy using insurance claims data in the US and reported that the annual total cost of care was $3419 (95% CI −$11,264 to −$4426) lower among patients in the CVD high risk group who used SGLT-2i [29]. The patients were classified according to the first drug used in the second-line therapy, and a pairwise comparison was performed between the SGLT-2i and DPP-4i groups using adjusted deciles of propensity score and Cox proportional hazards regression model, with treatment costs compared without any simulation. Studies that compare costs related to the use of specific drugs produce markedly different outcomes depending on the structure of the model, variables used, and the method of computing parameters. In our study, we focused only on hHF, the primary clinical outcome related to dapagliflozin using real-world data and the total cost was estimated using a simple model simulation by analyzing the cost incurred according to the incidence of hHF as opposed to the actual cost per drug group. Currently, five SGLT-2is—dapagliflozin, ipragliflozin, empagliflozin, canagliflozin, and ertugliflozin—are available in Korea; however, dapagliflozin was the only drug included in the national health insurance formulary during the patient enrollment period of this study, from September 01, 2015 to August 31, 2016. In the early days following the introduction of a novel class of drugs in clinical practice, treatment decisions are made on the basis of clinical trials of the drugs, so patients make prudent selections. Inevitably, there are differences between patients who use DPP-4i, which has significantly accumulated usage data, and those who choose dapagliflozin, which is a novel drug. Even if these differences are adjusted for statistically, the influence of unmeasured confounders cannot be completely eliminated. Moreover, as using insurance claims data is bound by limitations such as lack of detailed clinical documentation, misdiagnosis, and miscoding; it may be challenging to identify unmeasured confounders. Therefore, we

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used direct measurements of cost according to the incidence of hHF as the model parameter to minimize such influence, and for this reason, our model simulation computed cost incurred according to the risk for hHF by drug group.

A CVD event is a major cause of elevated medical cost for patients with DM. Garry et al. reported that among patients with high CVD risk, the total cost of care was higher for DPP-4i users than for dapagliflozin users [29], and our study also found that the difference in cost was higher among patients with underlying CVD. Thus, dapagliflozin may have maximal economic value when administered in patients with a high risk of a CVD event.

It is common for a typical economic evaluation to help decision making by presenting an increased amount of cost as a ratio as well as an increased effect (ICER) between alternatives. However, in this study, the analysis based on real-world data showed that dapagliflozin has an effect of reducing risk of hHF compared to DPP-4i, and even economical results of reducing medical costs, even though only by 2%. Ultimately, it supports that dapagliflozin is a dominant treatment strategy compared to DPP-4i. In countries with different health care systems, there may be quantitative differences in the economic performance of the same comparative alternative. This study is meaningful in that it estimated the amount of direct medical cost reduction due to a reduction in hHF risk in certain health care systems in Korea.

Our study had a few limitations. First, because it was a retrospective observational study, residual confounding factors could not be completely excluded, although we used propensity score weighting to adjust effects of confounders. In addition, our national claims data do not contain information concerning demographics such as diabetes duration, body mass index, or laboratory test results. Second, we relied on diagnostic codes for outcome ascertainment. However, a validation study reported that the overall positive predictive value of the ICD-10 codes was approximately 70%, compared with medical records reviews [44]. Moreover, mortality data were analyzed on the basis of diagnosis codes for the meddling, so it may differ from the actual mortality data. Third, this study used only hHF as the major clinical outcome and only compared direct medical costs incurred over 3 years. However, there are several other complications that contribute to the treatment cost of patients with DM, such as myocardial infarction, stroke, kidney complication, and premature death; and the duration of DM spans several decades. A long-term analysis including these major clinical outcomes need to be performed to more comprehensively compute the economic outcomes of a specific drug in order for the findings to serve as useful evidence for determining treatment strategies in clinical practice and devise health insurance financial policies.

## Conclusions

In conclusion, this study showed that dapagliflozin lowers the risk for hHF and subsequently, reduces direct medical costs as compared to DPP-4i. The protective effect against hHF was more evident among patients with underlying CVD.

**Authors' contributions**
JMS designed the study, analyzed data, and wrote the manuscript. JJK contributed to the design and data analysis for the economic analysis. HJK and HSS designed the study, analyzed data, contributed to the discussion, and reviewed the manuscript as a corresponding author. All authors qualify for authorship according to International Committee of Medical Journal Editors criteria and gave final approval for publication. All authors read and approved the final manuscript.

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